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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHLIENTZ, LEAH H	

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1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,690	LEGRAND ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,13-22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/492,129.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/7/2009 has been entered.

Priority

Acknowledgement is made of Applicant's claim for priority as a continuation-in-part of Application No. 10/492,129, in view of the petition decision mailed 7/29/2009. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 10/492,129, filed on 7/19/2004.

Status of Claims

Claims 1 and 9 have been amended. Claims 1-10, 13-22 and 24 are pending and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments filed 7/7/2009 have been considered but are moot in view of the new ground(s) of rejection. Any rejection not reiterated herein has been withdrawn.

Claim Rejections - 35 USC § 112

Claims 1-10, 13-22 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a microparticulate oral pharmaceutical dosage for delayed and controlled release of at least one active principle, excluding perindopril, this AP having an absorption window that is essentially limited to the upper parts of the gastrointestinal tract, wherein said dosage form comprises reservoir microcapsules that are each coated with at least one film coating comprising: at least one hydrophilic polymer A carrying groups that are ionized at neutral pH, and at least one hydrophobic compound B; wherein the release of the AP is governed by two different triggering mechanisms, wherein the first triggering mechanism releases the at least one AP based on a variation in pH and wherein the second triggering mechanism releases the at least one AP after a predetermined residence time in the stomach, wherein the dissolution behavior in vitro is such that at a constant pH of 1.4, the dissolution profile includes a

latency phase with a duration less than or equal to five hours, and the change from 1.4 to 6.8, results in a release phase that starts without a latency period. Dependent claims provide limitations wherein the mass fraction of the coating film is less than 40 percent, the microcapsules have a diameter of more than 200 microns and less than or equal to 2000 microns, the weight ratio B/A is between 0.45 and 1.0.

Accordingly, the claims are drawn to a broad range of hydrophilic polymer and certain hydrophobic compounds in a range of ratios and mass fraction of coating on the microcapsules having a certain functional in vitro release profile. However, Applicant has only provided very few examples of a specific hydrophilic polymer (Eudragit L) and specific hydrophobic compound (hydrogenated palm oil) in a ratio of 0.66 coated on an inert core including specific active agents metformin and acyclovir (see Examples 1-3). Applicant has not provided an adequate description of a reasonable number of species within the claimed genus to demonstrate that Applicant was in possession of full scope of the genus of dosage formulations that are claimed. It is noted that Applicant lists and claims a variety of additional hydrophilic polymers and hydrophobic compounds which may be suitable. However, based on the single limited example and the broad variability of multiple components within the claims, there would be undue experimentation for one of ordinary skill to arrive at the claimed functional dissolution properties from such a broad range of components, which may vary in ratio, percentage of mass fraction of coating, size of microparticle. This interpretation is supported by EP 1101490, which teaches spray coating a mixed film of stearic acid (i.e. hydrophobic compound) – Eudragit L 100 (methacrylic acid-methylmethacrylate polymer, hydrophilic)

in a ratio of 1:1 and having a coating mass fraction of 30%. Figure 4 shows lag time at pH 6.8 (approximately 2 hours). EP 1101490 describes suitable hydrophobic compounds include palmitic acid, hydrogenated castor oil, etc. as equivalent to stearic acid (paragraph 26). Thus, EP 1101490 formulations provide a teaching meeting the requisite structural features of the instant claims, however, the formulation provides different dissolution properties.

Based on the EP 1101490 reference, even formulations that that meet all of the physical/structural characteristics of Applicant's formulation (i.e. hydrophobic compound/hydrophilic polymer within the claimed ratio and coated on a microsphere of same size within the same mass fraction as that which is claimed), such formulations do not necessarily arrive at Applicant's claimed functional dissolution properties (i.e. the formulation of Example 3 of EP 1101490 has a lag time at pH 6.8, while Applicant claims no lag time). In view of the foregoing, the claims lack adequate written description of the full scope of formulation which is claimed, especially since the full scope of the genus of claimed structural features are not consistent with art-recognized functional properties. For example, one of ordinary skill would have to test a wide variety of hydrophilic polymers in combination with a wide variety of hydrophobic compounds, in widely varying ratios, and in various mass fraction of coating on a microparticulate core, yet based on the EP 1101490 reference, even formulations that meet all of the claimed structural requirements would not necessarily result in the claimed functional dissolution times at pH 1.4 and 6.8. The disclosure of a single example of hydrogenated palm oil-Eudragit L100 at a ratio of 0.66 is provided, however

a broad range of hydrophilic polymer/hydrophobic compounds in a broad ratio and coating mass fraction are claimed. Applicant has not provided a description to show a structure/functional correlation between the scope of the genus of formulations which are claimed and their resulting functional dissolution properties. In view of the data from the EP 1101490 reference, there is no evidence that Applicant provided an adequate description of a reasonable number of species within the claimed genus to show that Applicant was in possession of the full scope of formulations having the claimed functional dissolution properties. See MPEP 2163.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 13-22 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 12-41 of copending Application Serial No. 10/996,780. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to microparticulate oral formulations including dissolution behavior such that at 1.4, there is a latency period of less than or equal to five hours and the change from pH 1.4 to 6.8 (about 7) results in a release phase that starts without a latency period, wherein the formulation includes hydrophilic polymer A and hydrophobic polymer B within the same claimed ratio and mass fraction of coating film. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-10, 13-22 and 24 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 18-23 of copending Application Serial No. 11/449,675. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to microparticulate oral formulations including dissolution behavior such that at 1.4, there is a latency period of less than or equal to five hours and the change from pH 1.4 to 6.8 (about 7) results in a release phase that starts without a latency period, wherein the formulation includes hydrophilic polymer A and hydrophobic polymer B within the same claimed ratio and mass fraction of coating film. Accordingly, the claims

are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-10, 13-22 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 89-117 of copending Application No. 11/707,034. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to microparticulate oral formulations including dissolution behavior such that at 1.4, there is a latency period of less than or equal to five hours and the change from pH 1.4 to 6.8 (about 7) results in a release phase that starts without a latency period, wherein the formulation includes hydrophilic polymer A and hydrophobic polymer B within the same claimed ratio and mass fraction of coating film. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-10, 13-22 and 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-40 of copending Application No. 11/791,466. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to microparticulate oral formulations including dissolution behavior such that

at 1.4, there is a latency period of less than or equal to five hours and the change from pH 1.4 to 6.8 (about 7) results in a release phase that starts without a latency period, wherein the formulation includes hydrophilic polymer A and hydrophobic polymer B within the same claimed ratio and mass fraction of coating film. Accordingly, the claims are overlapping in scope and are obvious variants of one another. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 14, 15, 20-22 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Bartholomaeus *et al.* (US 2002/0176888).

Bartholomaeus discloses controlled release oral dosage formulation of a salt-forming active ingredient, wherein the active ingredient is present as at least two different salts in a solid aggregation state, wherein the two different salts have different water solubility and release the active ingredient in vitro at different release rates (abstract). Active substance includes morphine (paragraph 0015). Controlled total als

as release of the active substance can be modified in that at least one of the active substance salts may be present in retarded form (paragraph 0021). Retardation is provided by a retarding coating (paragraph 0022). It is possible to use mixtures of hydrophilic and hydrophobic material as retarding matrix material (paragraph 0036). Gastric juice resistant coatings such as Eudragit L, hydroxypropylmethyl cellulose acetate, cellulose acetate phthalate, etc. are also disclosed (paragraph 0038), and may be used in combination with suitable softeners (paragraph 0039). The oral dosage form is present in microparticulate form, optionally filled into capsules or compressed into tablets (paragraph 0043). Microparticles range in size from 30 to 200 micron (paragraph 0046). In example 1, pellets with a particle size of 800 to 1250 micron are coated with a coating comprising polymethacrylic acid methacrylate (equivalent to instantly claimed hydrophilic polymer A) and glycerine monostearate (equivalent to instantly claimed hydrophobic compound B, glyceryl stearate). Upon coating, pellets had a 7.6% weight increase relative to starting weight. See Table 1 and Figure 1. Release profile was determined at pH 7.2 (paragraph 0075). While no measurements were made at pH 1.2, regarding the claimed latency phase (less than or equal to 5 hours), the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and

to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Bartholomaeus discloses microparticles meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that the compositions would inherently have the claimed functional properties.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10, 13-22, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Santus *et al.* (US 5,405,619).

Santus discloses a controlled release pharmaceutical dosage form including a) microgranules of a pharmaceutical and an excipient, b) a plurality of polymeric lipidic

and wax-like coatings applied to the microgranules, the coated microgranules having dimensions which allow suspension of the coated microgranules in a liquid administration vehicle, and c) a liquid administration vehicle for the coated microgranules (abstract). The controlled release therapeutic system includes 1) controlled release form of an active ingredient, particularly theophylline, having dimensions comprised between 50 and 500 mcm, able to easily remain in suspension in a liquid for long periods, including: 1.1) an active ingredient suitably transformed by means of excipient into a microgranular nucleus having well defined technological and morphological characteristics, which are essential to assure the reproduceability and the uniform distribution of the successive film layers; 1.2) a first coating in contact with the microgranular nucleus for the purpose of forming a barrier insensitive to pH variations; 1.3) a series of successive coatings overlaying the first, which, while keeping the dimensions of the granules in the predetermined limits, constitute an alternation of layers of a hydrophilic and lipophilic character, which can be regulated in number and succession so as to be adapted to the pharmacological characteristics of the active ingredient employed. The therapeutic response is thus optimized and, at the same time, the complete dispersibility of the coated microgranules, at the moment of their suspension in the liquid vehicle is obtained (column 3, lines 54- column 4). Suitable actives include anti-inflammatory, etc. (column 4, line 54). Naproxen is also disclosed (Table 5). Excipients include lactose, microcrocrystalline cellulose, etc. (column 4, lines 58+). The first coating may include carboxyl-methyl-cellulose acetate, carboxyl-methyl-cellulose acetate butyrate and similar, or copolymers of esters of methacrylic and acrylic

acid, methyl methacrylates and similar, with a second component consisting of hydrogenated or partially hydrogenated cotton, soy-, arachid-, castor- oil and similar (column 5, lines 5-15). Successive coatings may include a lipophilic component layer of fatty acid. A suitable hydrophilic component may be cellulose acetophthalate, hydroxypropylmethylcellulose phthalate, etc. (column 5, lines 16-40). The film coating consists of a first layer deposited on a granulate, followed by succession of one or more superimposed layer consisting of lipophilic and hydrophilic suitably alternated materials, the sequence and number of layers are basically determined by the characteristics of the active active and the desired release of the active. As examples, we list combinations such as a)-e) (column 5-6). Examples of granules are shown in column 7. Examples of coating layers include one of components a), b) and c) in column 7-8 such as hydrogenated castor oil and ethylcelluose for a), cellulose acetate phthalate for b), and glyceryl monostearate, beeswax, cetyl alcohol for c). See Tables 1-3 describing various formulations A-G. See also Table 4, such as formulations including H = a/b, I = a/b/c/b, L – a/b/c/b/c/b. It is evident that by alternating hydrophilic and lipophilic layers, one can advantageously change rate of dissolution. Tests were performed at pH 7.4.

While Santus does not specifically recite that the mass fraction of the coating is less than 40% of the microgranule, it is taught that a high amount of waxes (50-60% of the total granule weight) go beyond the predetermined dimension limits for the coated microgranule (Table 2). Accordingly it would have been obvious to one of ordinary skill in the art at the time of the invention to provide coatings within the claimed mass fraction in order to provide microgranules within the claimed size range. With regard to

the weight ratio of B/A, while Santus does not specifically identify the amount of CAP and hydrophobic used in each formulation in tables 1-5, column 8 provides amount of CAP as 5 g and glyceryl monostearate as 9 g, and teaches using alternating layers of b) and c), usually the last layer consists of solution b). As such, it would be reasonable to use amounts such as 5 + 5 = 1.0 g CAP and 9 g glyceryl monostearate, such as in a layered coating comprising b/c/b for example, thus a B/A ratio of 0.9. While no measurements were made at pH 1.2, regarding the claimed latency phase (less than or equal to 5 hours), the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. The claims are descriptive and thus would be an inherent property of the claimed composition. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Since Santus discloses microparticles meeting the structural requirements of the instant claims, it is interpreted absent evidence to the contrary that the compositions would be capable of achieving the claimed functional properties.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS